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Research Article

Primary Antiphospholipid Syndrome Emerging During Long-term Aromatase Inhibitor Therapy: A Clinical Case Report

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Abstract

Aromatase inhibitors (AIs) are the standard adjuvant therapy for hormone-receptor–positive breast cancer in postmenopausal women and are considered less thrombogenic than tamoxifen. However, rare autoimmune complications, including lupus-like syndromes, inflammatory arthritis, and hepatitis, have been described. Antiphospholipid syndrome (APS), an autoimmune prothrombotic disorder is exceedingly rare in patients taking aromatase inhibitors. We present the case of a 68-year-old woman with breast cancer treated with surgery, chemotherapy, and letrozole for 3 years who subsequently developed deep venous thrombosis, ischemic stroke, severe thrombocytopenia, severe gastrointestinal bleeding, and triple-positive antiphospholipid antibody profile consistent with primary APS. Laboratory and imaging work-up excluded secondary causes of thrombosis such as systemic lupus erythematosus, bone marrow disease, metastatic cancer and heparin-induced thrombocytopenia. Her course was further complicated by refractory gastrointestinal bleeding which continued even after discontinuation of low-molecular-weight heparin (LMWH). Bleeding resolved only after argon plasma coagulation (APC). Because of ongoing thrombosis risk, anticoagulation was transitioned from LMWH to warfarin, and hydroxychloroquine was initiated, resulting in platelet stabilization ($23 \rightarrow 145 \times 10^9$/L). She had no further bleeding, and no recurrent thrombotic events. This case presents the clinical course, diagnostic work-up, and management of primary APS emerging during prolonged aromatase inhibitor therapy and summarizes relevant considerations for evaluation of thrombosis and thrombocytopenia in patients treated with endocrine therapy for breast cancer.

Keywords

Antiphospholipid Syndrome, Aromatase Inhibitor, Letrozole, Thrombocytopenia, Argon Plasma Coagulation, Warfarin, Hydroxychloroquine, Breast Cancer

1. Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia defined by recurrent arterial or venous thrombosis or pregnancy morbidity, accompanied by persistent antiphospholipid antibodies: lupus anticoagulant (LA), anticardiolipin (aCL), or anti-β_2-glycoprotein I (anti-β_2GPI) [1]. While APS may be classified as primary or secondary to

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systemic autoimmune disorders, there is growing recognition of medication-induced autoimmune dysregulation.

Aromatase inhibitors (AIs)—including anastrozole, letrozole, and exemestane—effectively suppress peripheral estrogen synthesis and form the cornerstone of adjuvant endocrine therapy for hormone receptor-positive breast cancer. Compared to tamoxifen, AIs have significantly lower thrombotic risks) [6]. Nonetheless, they have been associated with various autoimmune manifestations, such as cutaneous lupus [7], autoimmune hepatitis [8], and inflammatory arthropathies. The question of whether AIs can induce or unmask APS remains unclear but is biologically plausible given the immunomodulatory roles of estrogen [5].

In this report, we present a case of primary APS emerging during long-term AI therapy in a breast cancer survivor, characterized by the development of both venous and arterial thromboses, severe thrombocytopenia, and gastrointestinal bleeding. This case reveales the importance of considering rare autoimmune complications in oncology patients receiving prolonged targeted therapies and highlights challenges in their multidisciplinary management.

2. Case Presentation

2.1. Oncologic Background

The patient, a 68-year-old woman, presented with a complex medical history that included hypertension, type 2 diabetes mellitus, and hypothyroidism. In June 2021, she received a diagnosis of left breast invasive carcinoma. Pathological analysis of her tumor revealed an estrogen receptor (ER) positivity of 100%, progesterone receptor (PR) positivity of 10%, human epithelial growth factor receptor 2 (HER2) negativity, and antigen Ki-67 proliferation index of 30%. This hormonal profile categorized her cancer as hormone-receptor positive, a subtype that typically responds well to endocrine therapies, but the relatively high Ki-67 index, also indicated a need for aggressive initial treatment. She has comorbidities of hypertension and type 2 diabetes, well-established risk factors for cardiovascular disease, which later proved relevant in her clinical course. Notably, she reported no personal or familial history of thrombosis, miscarriages, or autoimmune rheumatic diseases, making her subsequent presentation particularly striking.

Her initial treatment regimen commenced with four cycles of doxorubicin–cyclophosphamide, a standard anthracycline- and alkylating agent-based chemotherapy combination for early-stage breast cancer aimed at reducing tumor burden and eradicating micrometastatic disease. Following the completion of this regimen, she transitioned to weekly paclitaxel, a taxane-based chemotherapy known for its efficacy in breast cancer. However, after only her second dose of paclitaxel in December 2021, she developed acute swelling in her right leg. A diagnostic Doppler ultrasound confirmed the presence of deep venous thrombosis (DVT), a recognized complication in cancer patients, often exacerbated by chemotherapy-induced hypercoagulability or the inflammatory state associated with the malignancy itself. To manage this DVT, rivaroxaban, a direct oral anticoagulant (DOAC), was initiated at a dose of 15 mg/day and planned for a 6-month course.

The patient's chemotherapy regimen was subsequently discontinued due to refractory hypertension, a challenging side effect that can be exacerbated by certain chemotherapeutic agents and pre-existing cardiovascular comorbidities. Following chemotherapy discontinuation, she underwent a total left mastectomy, achieving surgical control of her primary breast cancer. Post-surgery, she began adjuvant endocrine therapy with letrozole, an aromatase inhibitor. Letrozole is a non-steroidal AI that functions by reversibly binding to the aromatase enzyme, thereby inhibiting the conversion of androgens to estrogens in peripheral tissues and in the tumor itself. This therapy was intended for a duration of 3 years to reduce the risk of breast cancer recurrence.

2.2. Ischemic Stroke (August 2025)

In August 2025, approximately three years into her letrozole therapy, the patient experienced a sudden onset of dysarthria (difficulty speaking) and right-sided weakness. Clinical examination revealed neurological deficits consistent with an acute stroke, including right central facial palsy, right hemiparesis (weakness on one side of the body), and a positive Babinski sign, indicative of an upper motor neuron lesion.

To identify the underlying vascular pathology, a CT angiography was performed. This imaging study demonstrated severe arterial disease, specifically a 90% stenosis of the right common carotid artery, a major vessel supplying blood to the brain. Furthermore, it identified a partial filling defect in the left middle cerebral artery (MCA) sphenoidal segment, suggesting a compromised blood flow or thrombotic occlusion in this crucial cerebral artery. A subsequent brain magnetic resonance (MRI) (Figure 1) confirmed the presence of multiple lacunar ischemic lesions within the MCA territory. Lacunar infarcts are typically small, deep infarcts that result from occlusion of a single penetrating artery, often associated with chronic hypertension and diabetes—conditions that were present in this patient.

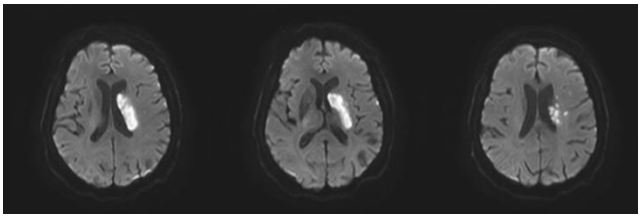

Figure 1. *Brain MRI - presence of multiple lacunar ischemic lesions within the MCA territory.*

Laboratory values obtained at the time of stroke presenta-

tion revealed several abnormalities: a mild anemia with red blood cell (RBC) 3.34 × 10^9/L; hemoglobin (Hb) 10.6 g/dL) and a notable degree of thrombocytopenia (platelets 77 × 10^9/L). Markers of inflammation and coagulation were elevated, with fibrinogen at 653 mg/dL and D-dimer at 1.75 µg/mL. Her thyroid-stimulating hormone (TSH) was elevated at 9.5 mU/L, consistent with hypothyroidism, while her glycosylated hemoglobin (HbA1c) 6.7%. Renal and hepatic functions were within normal limits, and routine coagulation parameters like Prothrombine Time, activated partial thromboplastine time, international ratio (PT/aPTT/INR) were unremarkable, suggesting that the primary issue was not an intrinsic clotting factor deficiency. Given the acute ischemic event and the presence of underlying thrombotic tendencies, treatment with low molecular weight heparin (LMWH) was initiated.

2.3. Hospital Admission with GI Bleeding (September 2025)

One month later, in September 2025, while receiving LMWH for stroke prevention, the patient was admitted to the hospital due to hematemesis, melena, dizziness, extreme fatigue that impaired her daily activities, requiring assistance from her family members. Examination findings on admission were: pale skin, heart rate 108/ min and O2SAT 90%.

Admission laboratory results confirmed the severity of the bleeding and its impact on her hematologic status:

1) RBC (red blood cell): 2.62 × 10^9/L (further decline from previous measurement)
2) Hemoglobin (Hb): 7.7 g/dL
3) Platelets: 34 × 10^9/L (a significant drop, with a lowest level at 23 × 10^9/L)
4) Ferritin: 1190 ng/mL
5) Normal PT/aPTT/INR (Prothrombin time/ activated partial thromboplastin/International ratio)
6) Normal tumor markers carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19- 9), cancer antigen 125 (Ca 125) and cancer antigen 15-3 (CA 15-3) ruling out cancer recurrence as the cause of bleeding.

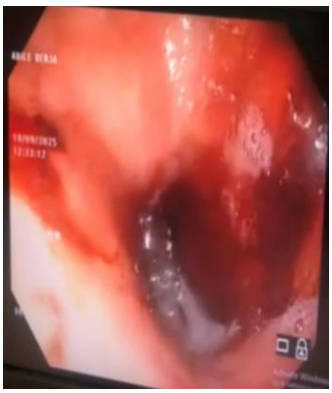

Figure 2. *fibrogastroscopy – multiple vascular ectasias with active bleeding.*

An urgent upper endoscopy was performed, revealing multiple vascular ectasias with active bleeding within the gastrointestinal tract (Figure 2). These lesions, often fragile, are prone to bleeding, especially in the presence of anticoagulation or underlying coagulopathies. The bleeding ectasias were successfully treated with argon plasma coagulation (APC) (Figure 3), a thermal endoscopic technique used for achieving hemostasis. Repeated sessions were necessary to achieve complete hemostasis, highlighting the persistent nature of the bleeding.

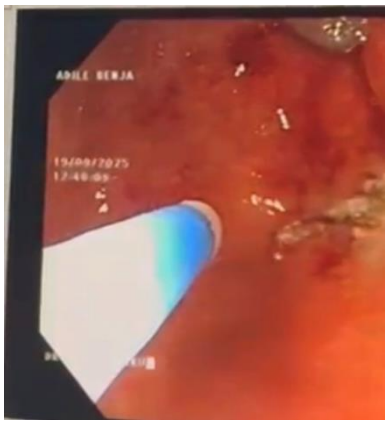

Figure 3. *Gastric hemostatis achieved with argon plasma coagulation.*

Despite successful endoscopic management of the bleeding, the severe thrombocytopenia persisted, with platelet counts fluctuating between 30–50 × 10^9/L. Given the critical nature of this finding, a thorough work-up was initiated to determine the cause of thrombocytopenia. Bone marrow aspiration and immunophenotyping were performed, which successfully excluded marrow infiltration by malignancy, myelodysplastic syndromes, or any primary hematologic disorders. This step was crucial to rule out alternative causes of her profound thrombocytopenia. The platelet trend over the first two weeks of this admission is depicted in Figure 4, illustrating a persistent critically low count.

2.4. Autoimmune Work-up

The confluence of recurrent thrombotic events (DVT, ischemic stroke), persistent and severe thrombocytopenia, and the absence of clear secondary causes for these pathologies prompted an extensive investigation for autoimmune thrombophilia. The autoimmune work-up yielded significant findings:

1) Antinuclear Antibody (ANA): 1:1280
2) Lupus Anticoagulant (LA): 125 seconds (normal range 0–44 seconds).
3) Anti-β_2-Glycoprotein I (anti-β_2GPI): IgM 31 U/mL (0-5) and IgA 50 U/mL (0-20)
4) Anticardiolipin (aCL) IgM: 40 U/mL (normal range 0–7

U/mL)
5) Antiphospholipid (aPL) IgM: 23 U/mL (0-10)
6) Complement Levels: C3 44 mg/dL (83-193) and C4 10 mg/dL (15-57)
7) Anti double stranded DNA (Anti-dsDNA): negative
8) Platelet factor 4 antibody (Anti-PF4): negative (excluding Heparin-Induced Thrombocytopenia (HIT), which was a vital distinction given her prior LMWH exposure).

Drug-induced thrombocytopenia was considered unlikely, as the patient had no history of taking medications known to reduce platelet counts, and no new drugs had been introduced before the onset of thrombocytopenia.

These comprehensive findings confirmed a diagnosis of triple-positive primary APS, characterized by the presence of lupus anticoagulant, anticardiolipin antibodies, and anti-β_2GPI antibodies. This triple positivity is recognized as the highest-risk phenotype for recurrent arterial events and is associated with a poorer prognosis [4]. Platelet trend over two weels is shown in Figure 4.

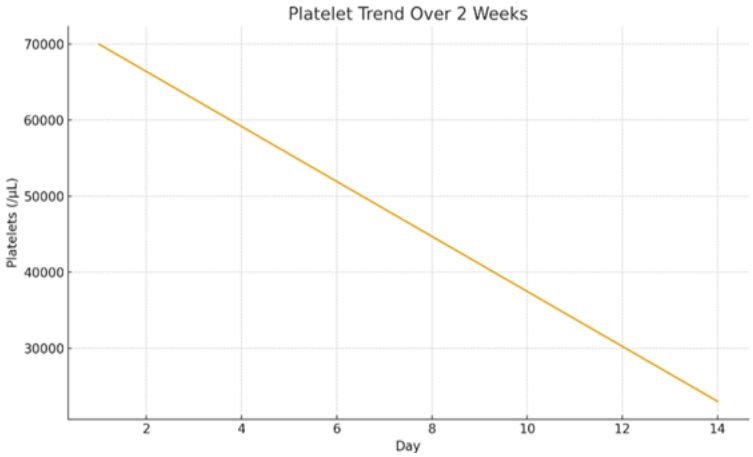

Figure 4. *Platelet trend over 2 weeks.*

3. Management and Treatment

Because LMWH contributed to gastrointestinal bleeding and platelet decline, anticoagulation was discontinued. After endoscopic hemostasis, the patient was transitioned to warfarin (INR goal 2–3), consistent with evidence favoring vitamin-K antagonists in high-risk APS [3, 9].

She was additionally treated with:
1) Hydroxychloroquine 200 mg/day
2) Low-dose corticosteroids 20 mg /day initially, tapered thereafter in subsequent doses 10 mg/day, 7.5 mg and 5 mg. They were stopped when the platelet number was normal.

After 2 weeks:
1) Platelets improved to 145 $\times 10^9$/L
2) No further GI bleeding
3) No new thrombotic events

Platelet recovery after therapy is shown in Figure 5.

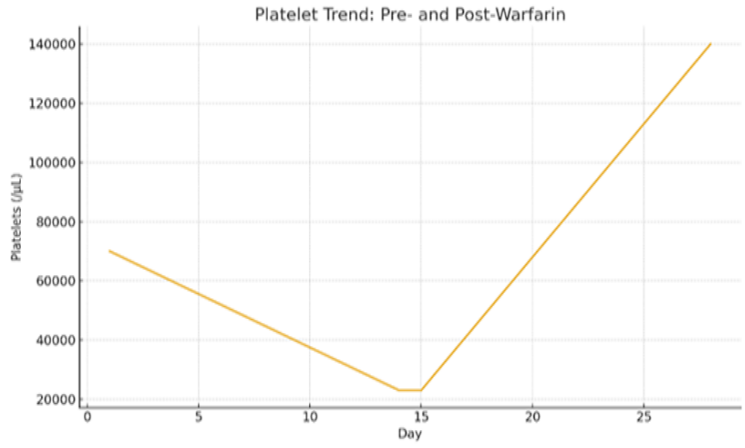

Figure 5. *Platelet trend Pre- and Post-Warfarin.*

4. Discussion

This case fulfils international APS criteria: objective venous thrombosis, arterial stroke, and persistent aPL antibodies measured ≥12 weeks apart [1]. Moreover, the patient displayed triple positivity (LA + aCL + anti-β_2GPI), the highest-risk phenotype associated with recurrent arterial events and poorer prognosis [4].

4.1. Aromatase Inhibitors and Autoimmunity

AIs generally have a safer thrombotic profile than tamoxifen [6]; however, autoimmune reactions including cutaneous lupus [7] and autoimmune hepatitis [8] have been documented. Several possible hypotheses exist:

4.2. Estrogen Deprivation and Endothelial Dysfunction

Estrogen exerts protective effects through:
1) upregulation of nitric oxide synthase
2) antioxidant activity
3) anti-inflammatory modulation

AI-induced estrogen depletion may increase endothelial susceptibility to injury, especially in patients with preclinical autoimmune disorders [5].

4.3. Immune Dysregulation

Estrogen modulates both innate and adaptive immunity. Withdrawal may:
1) shift cytokine balance toward a pro-inflammatory profile
2) reduce regulatory T-cell function
3) enhance autoantibody production

These effects could unmask latent APS or accelerate autoantibody expression [10].

4.4. Interaction with Chemotherapy-induced Endothelial Damage

Her earlier DVT during paclitaxel treatment may have:
1) initiated endothelial injury
2) triggered exposure of phospholipid antigens
3) promoted autoantibody production

APS onset after chemotherapy is documented in rare cases.

4.5. Synergistic Risk Accumulation

Multiple factors converged:
1) age
2) estrogen deprivation
3) endothelial injury
4) autoimmune predisposition

This constellation substantially increases thrombotic risk.

4.6. Thrombocytopenia in APS

Thrombocytopenia occurs in up to 40% of APS patients and is typically mild. Severe thrombocytopenia, as in this case (23×10^9/L), may reflect complement-mediated platelet destruction, immune activation, or consumption. LMWH-associated HIT was excluded (negative anti-PF4). Platelet improvement following warfarin supports control of APS-mediated immune activity rather than bone-marrow pathology.

4.7. Anticoagulation Strategy

Randomized trials show that DOACs are inferior to warfarin in high-risk APS, particularly triple-positive patients and those with arterial events [3, 9]. Therefore, lifelong warfarin is recommended in such cases [2].

5. Conclusion

This case demonstrates a rare presentation of primary antiphospholipid syndrome emerging during long-term aromatase inhibitor therapy. Clinicians should consider APS when encountering unexplained thrombosis or thrombocytopenia in breast cancer patients on AIs. In high-risk APS, warfarin remains the preferred long-term anticoagulant, and hydroxychloroquine may contribute to improved platelet stability.

Abbreviations

AI	Aromatase Inhibitors
APS	Antiphos Philipid Syndrome
APC	Argon Plasma Coagulation
ER	Estrogen Receptor
PR	Progesterone Receptor
HER	Human Epithelial Growth Factor Receptor 2
Ki-67	Marker of Proliferation Kiel 67
DVT	Deep Vein Thrombosis
DOAC	Direct Oral Anticoagulant
MCA	Middle Cerebral Artery
RBC	Red Blood Cell
Hb	Hemoglobin
MRI	Magnetic Resonance
TSH	Thyroid Stimulating Hormone
HbA1c	Glycosylated Hemoglobin
PT/aPTT/INR	Prothrombin Time /Activated Partial Thromboplastine Time
LMWH	Low Molecular Weight Heparine
O2sat	Oxygen Saturation
CEA	Carcinoembryonic Antigen
Ca 19-9	Carbohydrate Antigen 19-9

Ca 125	Cancer Antigen 125
Ca 15-3	Cancer Antigen 15-3
ANA	Antinuclear Antibody
LA	Lupus Anticoagulant
Anti β2-Glycoprotein	Anti Beta 2 Glycoprotein Antibody
IgM	Imunoglubulin M
aCL	Anti Cardiolipin Antibody
aPL	Antiphospholipid Antibody
C3 C4	Complement
Anti ds DNA	Anti double stranded DNA Antibody
Anti PF4	Platelet Factor 4 Antibody
HIT	Heparin Induced Thrombocytopenia

Conflicts of Interest

The authors declare no conflicts of interest.

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